

## DOCTORAL THESIS

### Neuroprotective effects and underlying mechanisms of Chinese medicinal compounds in Parkinson's disease models

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**Neuroprotective Effects and Underlying  
Mechanisms of Chinese Medicinal Compounds in  
Parkinson's Disease Models**

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**A thesis submitted in partial fulfillment of the requirements**

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## ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting 2% of the population over 65 years old. The biochemical and molecular mechanisms leading to dopaminergic neuronal degeneration in PD remain unclear. However, a large body of evidence suggests that oxidative stress and abnormal protein aggregation are two critical factors contributing to the pathogenesis of PD.

6-Hydroxydopamine (6-OHDA), an analog of the neurotransmitter dopamine, is widely used to induce PD-like damages in animals as well as in cells, and has been used to test neuroprotective effects of multiple anti-PD drugs. In this study, 6-OHDA was used to induce SH-SY5Y cells toxicity as a cellular PD model for the screening of anti-PD compounds derived from Chinese herbal medicines. Our study revealed that baicalein, a flavonoid extracted from Chinese herbal medicine Huangqin (*Scutellaria baicalensis* Georgi), inhibited 6-OHDA-induced cell death in human neuroblastoma SH-SY5Y cells, probably via stabilizing the intracellular calcium homeostasis.

Abnormal protein aggregation and accumulation in the brain have been linked to the pathogenesis of neurodegenerative diseases including PD. Recent studies suggested that the oligomeric form of aggregates may represent the most toxic species, and thus could be a good therapeutic target. Our study revealed that baicalein inhibited both oligomerization and fibrillation of alpha-synuclein ( $\alpha$ -syn) *in vitro* and prevented the formation of  $\alpha$ -syn oligomers in neuronal cells. Baicalein also protected SH-SY5Y cells from  $\alpha$ -syn oligomer-induced toxicity. Our study indicates that baicalein is a good inhibitor of  $\alpha$ -syn aggregation and toxicity.

One of the strategies for the treatment of neurodegenerative diseases is to promote the clearance of abnormal protein aggregates in the neurons. Autophagy-lysosome system is a major mechanism for the degradation of large protein aggregates in the cells, thus

seeking potent autophagy enhancers to promote the degradation of pathogenic protein aggregates could be a strategy to identify therapeutic agents for neurodegenerative diseases. Our study identified a potent autophagy inducer-isorhynchophylline (IsoRhy), an alkaloid isolated from herbal medicine Gouteng (*Uncaria rhynchophylla* (Miq.) Jacks). IsoRhy induced massive autophagy in neuronal cells (N2a, SH-SY5Y, PC12 and primary neuron) as well as in the brain of *Drosophila*; IsoRhy promoted degradation of wild type & mutant alpha-synuclein monomers, alpha-synuclein oligomers and alpha-synuclein/synphilin-1 aggresomes in neuronal cells via autophagy-lysosome pathway; IsoRhy Induced autophagy in N2a cells in a mTOR-independent but beclin-1-dependent manner.

Given the role of oxidative stress and abnormal protein aggregation in neurodegenerative diseases including PD, our results suggest that baicalein and IsoRhy, the bioactive compounds isolated from Chinese herbal medicine, may have potential to be developed into therapeutic agents for the treatment of these devastating disorders.

**Keywords:** Abnormal protein aggregation, Alpha-synuclein, Autophagy, Baicalein, Isorhynchophylline, Parkinson's disease, 6-hydroxydopamine,

## TABLE OF CONTENTS

DECLARATION .....	i
ABSTRACT .....	ii
ACKNOWLEDGEMENTS .....	iv
TABLE OF CONTENTS .....	v
LIST OF FIGURES .....	ix
LIST OF ABBREVIATION .....	xii
CHAPTER 1 Introduction.....	1
1.1 Parkinson's disease.....	1
1.2 Epidemiology of PD.....	2
1.3 Pathology of PD .....	3
1.4 Etiology of PD.....	4
1.5 Therapeutic potential of Traditional Chinese Medicine in the treatment of PD .....	17
CHAPTER 2 Hypothesis and Objectives.....	19
CHAPTER 3 Baicalein prevents 6-OHDA/SCORBIC Acid -Induced SH-SY5Y Cell Death via Stabilizing Intracellular Calcium Homeostasis.....	24
3.1 Introduction .....	24
3.2 Materials and Methods .....	28
3.2.1 Reagents .....	28
3.2.2 Cell culture and drug treatments .....	29
3.2.3 6-OHDA degradation assay.....	29
3.2.4 Cell viability and cytotoxicity assay .....	30
3.2.5 DAPI staining .....	30
3.2.6 Calcium imaging .....	31
3.2.7 Measurement of intracellular ROS level.....	31
3.2.8 Flow cytometry .....	32
3.2.9 Statistical analysis .....	32
3.3 Results .....	33

3.3.1	6-OHDA toxicity on SH-SY5Y cells is greatly enhanced in the presence of ascorbic acid .....	33
3.3.2	Baicalein prevents 6-OHDA/AA-induced toxicity on SH-SY5Y cells .....	39
3.3.3	Baicalein prevents 6-OHDA/AA-induced intracellular calcium elevation in SH-SY5Y cells .....	46
3.3.4	6-OHDA/AA toxicity is independent of dopamine transporter (DAT) in SH-SY5Y cells.....	50
3.4	Conclusion and discussion.....	53
<b>CHAPTER 4 Baicalein Inhibits Formation of Alpha-synuclein Oligomers Within Living Cells and Prevents Beta-amyloid Peptide Fibrillation and Oligomerization .....</b>		
4.1	Introduction.....	59
4.2	Materials and Methods.....	62
4.2.1	Reagents.....	62
4.2.2	Sample preparation for the aggregation assays.....	63
4.2.3	Thioflavin-T (Th-T) fluorescence assay .....	63
4.2.4	Oligomeric ELISA .....	64
4.2.5	Cell culture and transient transfections.....	65
4.2.6	GN-aSyn/aSynGC fluorescence complementation assay .....	65
4.2.7	Cell imaging.....	66
4.2.8	Flow cytometry analysis .....	66
4.2.9	Native and denatured PAGE and immunoblotting.....	67
4.2.10	Inhibition and disaggregation of A $\beta$ fibrils by baicalein .....	68
4.2.11	Electron microscopy .....	69
4.2.12	Preparation of A $\beta$ oligomers and anti-oligomerization effect of baicalein .....	69
4.2.13	LDH assay.....	70
4.2.14	MTT assay .....	71
4.2.15	Data analysis .....	71

4.3	Results .....	72
4.3.1	Systematical comparison of anti-oligomeric and anti-fibrillar activities of 8 compounds extracted from Chinese herbal medicine on $\alpha$ -syn aggregation .....	72
4.3.2	Baicalein inhibits $\alpha$ -syn oligomerization in living cells.....	77
4.3.3	Baicalein inhibits A $\beta$ 1-42 fibril formation and disaggregates pre-formed A $\beta$ 1-42 fibrils .....	81
4.3.4	Baicalein inhibits A $\beta$ 1-42 oligomers formation.....	84
4.3.5	Baicalein alleviates the neurotoxicity of $\alpha$ -syn oligomers and A $\beta$ 1-42 fibrils .....	86
4.4	Conclusion and discussion .....	89
CHAPTER 5 Isorhynchophylline, An Alkaloid Extracted From Chinese Herbal Medicine Gouteng, Promotes the Degradation of Alpha-synuclein in Neuronal Cells via Inducing Autophagy .....		
5.1	Introduction .....	95
5.2	Materials and Methods .....	99
5.2.1	Reagents .....	99
5.2.2	Establishment of N2a cells constantly expressing GFP-LC3.....	100
5.2.3	Western blotting analysis.....	100
5.2.4	Cell imaging of fluorescent puncta .....	101
5.2.5	Flow cytometry analysis.....	102
5.2.6	Primary neuron culture.....	102
5.2.7	Transfection of primary neurons .....	104
5.2.8	Differentiation of human embryonic stem cells into dopaminergic neurons .....	104
5.2.9	Immunostaining.....	106
5.2.10	RNA interference assay .....	106
5.2.11	Statistical analysis .....	107
5.3	Results .....	108
5.3.1	IsoRhy induces autophagy in neuronal cell lines .....	108

5.3.2	IsoRhy induces autophagy in primary mice cortical neurons.....	117
5.3.3	IsoRhy promotes clearance of transient over-expression of $\alpha$ -syn in N2a cells via inducing autophagy.....	121
5.3.4	IsoRhy promotes the degradation of $\alpha$ -syn in human dopaminergic neurons differentiated from embryonic stem cells.....	128
5.3.5	IsoRhy induces autophagy in neuronal cells in an mTOR-independent and Beclin-1 -dependent manner. ....	130
5.4	Conclusion and discussion.....	133
CHAPTER 6 sorhynchophylline induces autophagy in <i>Drosophila</i> .....		137
6.1	Introduction.....	137
6.2	Materials and Methods.....	138
6.2.1	Reagents.....	138
6.2.2	<i>Drosophila</i> strains and culture .....	139
6.2.3	Drug feeding .....	139
6.2.4	Confocal imaging of GFP-atg8a puncta in the brain .....	139
6.2.5	LysoTracker staining.....	140
6.2.6	Western blotting analysis .....	140
6.3	Results.....	141
6.3.1	IsoRhy induces autophagy in L3 larvae fat body .....	141
6.3.2	IsoRhy induces autophagy in L3 larvae.....	143
6.3.3	IsoRhy induces autophagy in adult <i>Drosophila</i> brain.....	145
6.4	Conclusion and discussion.....	147
CHAPTER 7 General Discussion and Conclusion.....		150
References.....		155
Publications List .....		183
CURRICULUM VITAE.....		189